REMARKS

The issues outstanding in the Office Action mailed January 8, 2008, are the objection to the specification and the rejections under 35 U.S.C. 112. Reconsideration of these issues, in view of the following discussion, is respectfully requested.

Objections

At page 2 of the specification, it is argued that the specification is objectionable as not containing titles to distinguish separate sections. Although appropriate titles have been added, MPEP §601 (I) entitled "Guidelines for Drafting a Nonprovisional Patent Application Under 35 U.S.C. 111(a)" states that the arrangement in contents of the specification, including titles, is "preferable." It is thus submitted that titles are not required. However, in order to advance prosecution, said titles have been added. Withdrawal of the objection is therefore respectfully requested.

Rejection Under 35 U.S.C.

Claims "1-14" are listed at page 3 of the Office Action as being rejected under 35 U.S.C. 112, first paragraph. Inasmuch as the following paragraph is applied to claims 1-19, it is assumed that claims 15-19 are also subject to the rejection. Reconsideration of the rejection is respectfully requested.

It is argued, at page 3 of the Office Action, that the specification is enabling for compounds, compositions, derivatives and salts, but not for polymorphic forms, solvates or stereoisomers. Applicants respectfully disagree. First, with respect to polymorphs, claim 1 recites prodrugs, derivatives, solvates, stereoisomers or salts. Thus, despite the speculation in the Office Action, it is not seen that polymorphs are an issue. Of course, the compound, defined by formula I, covers all of its stereoisomers, polymorphs, etc. Inasmuch as the compounds themselves are enabled, as admitted at page 3 of the Office Action, it is not seen that the lengthy discussion of polymorphs at pages 3 and 4 of the Office Action is relevant.

With respect to the term "solvates", Applicants respectfully, albeit quite strongly, submit that the term is clearly enabled. It appears that the Office Action alleges that the formation of solvates is not enabled because, e.g., the formation of solvates is unpredictable. In support, the Office Action quotes a passage from *Vippagunta* which indicates that certain

predictions about solvates or hydrates of a compound are complex and difficult.

However, the Office Action appears to ignore within the same document the passages which show the claims are enabled. For example, *Vippagunta* on page 15, top of first column, states that

> It has been established that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. (Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement that

> Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling ... Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states that

> Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. ...
>
> The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* throughout the reference teaches various solvates, hydrates, etc., structural aspects thereof, examples thereof, including preparation techniques, and methods/techniques for the characterization thereof. See, e.g., pages 15-18.

While it may be true, that the prediction of what a particular solvate of a compound will actually look like, e.g., whether one, 3 ½, 6 or 12 solvent molecules are incorporated, the Office Action is incorrect with respect to the alleged lack of enablement.

Even the very paper cited in support of the rejection demonstrates that one of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing solvates and how such solvates would be identified or characterized, e.g., by polarized light microscopy, etc. See extensive list of techniques identified on column 2 of page 18.

Additionally, based on the above discussed statistics in this field provided by *Vippagunta*, one of ordinary skill in the art would also have a good expectation for success. While certain predictions may be difficult in the art of forming solvates, the formation of solvates is common with pharmaceutically active ingredients and methods of detecting and characterizing them are well-known and widely applied routinely.

In sum, *Vippagunta*, rather than supporting a lack of enablement rejection, supports the opposite, i.e., that there is no lack of enablement.

Thus, the Office Action has not carried its burden in establishing a lack of enablement because the Office Action has not established any basis to doubt objective enablement. See *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971) holding that a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (Emphasis added.) See also *In re Bundy*, 209 USPQ 48 (1981) holding that the "PTO must have adequate support for its challenge to the credibility of applicant's statements of utility," which statements were made in *Bundy* in the context of an enablement rejection, and which is lacking in the present case. In view of the state of the art, it is evident that there is no indication that one of ordinary skill in the art would have questioned that solvates could be formed. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005).

Nevertheless, applicants provide further information clearly demonstrating that solvate formation is a common phenomenon among pharmaceutical substances, i.e., Polymorphism: in the pharmaceutical industry (edited by *Ralf Hilfiker*; 2006 Wiley-VCH), Chapter 8, The Importance of Solvates, by *U. J. Griesser*, pp. 211-222 (hereinafter *Griesser*).

On page 220, *Griesser* teaches that

> Over almost two decades we carefully collected data on the solid-state properties of a few thousand pharmaceutically relevant organic compounds, with special focus on those drug substances listed in the Pharmacopoeia European (PhEur). The 1997 edition of PhEur contained 559 well-defined organic drug compounds. ... For more than 55% of them either polymorphs or solvates are known. In a newer evaluation of a larger set of data (PhEur edition 4.02, 8008 solid organic compounds ... this fraction increased only slightly to 57%. As shown in Fig. 8.4, 29% of the compounds are known to form hydrates, 10% other solvates ... (Emphasis added.)

Additionally, various factors in considering whether solvates would be expected to form are identified by *Griesser* on pages 220-221, e.g., salt forms, molecular size,

lipophilicity. A citation is provided for ascertaining "further trends and interrelations between molecular properties and solvate/hydrate formation." See the middle of page 221. All this demonstrates that one of ordinary skill in the art would know or have guidance as to what factors to consider in expectation of success.

Moreover, under the section titled "Generation and Characterization of Solvates" on page 222, *Griesser* teaches that

> Since it is imperative to establish the crystal forms of an active pharmaceutical ingredient (API) to satisfy the regulatory authorities ..., solvates of drug compounds are now preferentially discovered in systematic polymorph screenings. ... **Automated crystallization systems and strategies** have been developed to speed up this process, **allowing thousands of crystallization experiments in a short time**. (Emphasis added.)

In view of the state of the art of solvate formation, e.g., solvate formation being a very common phenomenon associated with drug substances, the generation and examination of which is done with highly automated machines, the Office Action has not established that it would require undue experimentation by one of ordinary skill in the art to prepare and even characterize the solvates of a compound.

While the amount of work to prepare solvates of the compounds of the invention may require some effort or maybe even considerable effort (although not admitted), no undue experimentation is required in the preparation of solvates. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988). One of ordinary skill in the art merely through routine laboratory efforts can take various compounds of the invention, which are explicitly admitted by the Office Action to be enabled at the top of page 3, bring them together with various solvents and check whether solvates have formed. This type of work is merely routine laboratory work and does not require undue experimentation. Moreover, as discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine," which it is in the present case.

Moreover, although it is recognized that the Hilfiker text is published in 2006, the

relevant passages that deal with the statistical aspects and frequency of solvates are (8.3, pp 219 ff.) based on data given in the Pharmacopoeia European (PhEur) which was published well before the priority date of the instant application, i.e. published in the 1997 (3rd edition), 2002 (4th edition) and February 2003 (supplement 4.02). According to this statistical data, solvates are common in the chemistry of pharmaceuticals and thus enabled. Additionally, the majority of the papers that are cited in the text are published before or around the priority date or the international filing date of the instant application. Thus, the review article in Hilfiker gives a clear picture what was known in the field of solvates around the priority/filing date of the instant application, and clearly supports enablement.

Moreover, attached to the present reply is secondary literature, i.e. articles cited as number 57, 63 and 64 in Hilfiker, and an article of U. J Griesser (Auer et al.), a co-author heavily cited by Hilfiker et al. The latter was received on July 20, 2003 and accepted in September 2003 and thus published in between the priority date and the international filing date of the instant application.

All those articles show that the skilled artisan was aware of solvates in the field of pharmaceutically active ingredients and that a plenty of methods for detecting them and producing them on a routine basis where already established before the priority/filing date of the instant application. Such methods include detection by infrared FT-Raman spectroscopy (e.g. in Auer et al.) and production by crystallization, spray drying and/or lyophilization (freeze-drying), see e.g. Otsaka et al and Yu et al.). Byrn et al even show flowcharts for the systematic approach to the detection of solvates as early as 1995. Additionally, the article by Byrn et al shows that information on the polymorphic forms (of which solvates are the most frequent ones) was routinely asked for by regulatory offices around the world, including the FDA. Moreover, e.g. on page 951, section D, Byrn et al state that regularly an anhydrous drug product obtained can be partially or completely converted into hydrates (the most common form of solvates) by a method as simple as wet grinding.

With respect to the preparation of stereoisomers, the comment on page 5 of the Office Action is not understood. One of ordinary skill in the art would clearly recognize that the claimed compounds contain chiral centers. One of ordinary skill in the art would also know, using only routine separation techniques, how to isolate a given stereoisomer. Inasmuch as such is clearly routine in the art, it is submitted that the specification clearly enables

preparation of stereoisomers of the compounds of formula I. Withdrawal of this portion of the rejection is therefore also respectfully requested.

In conclusion, it is submitted that the claims fully satisfy the requirements of 35 U.S.C. 112, and withdrawal of this one remaining issue is respectfully requested.

The claims of the application are submitted to be in condition for allowance. However, if the Examiner has any questions or comments, he is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,
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Attorney Docket No.: MERCK-3071

Date: May 8, 2008

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